

REMARKS**Claim Status**

Claims 35-68 are pending in the application. Claims 54-68 were withdrawn by the Examiner as being drawn to a non-elected invention. Claims 35-42, 45, 47, 49-52, 54-55, 58-59 and 68 have been amended.

Claim Amendments

Claim 35 has been amended to be directed to an isolated aldonic ester. Support for this amendment can be found throughout the application. For example, on page 1, paragraph 1, the specification states:

The present invention relates to aldonic acid esters, solids and solutions which comprise these esters, and methods for the production thereof.
(*Emphasis added.*)

on page 12, paragraph 4, the specification states:

Such aldonic acid esters can then be isolated as substance for coupling, for example for HESylation. (*Emphasis added.*)

on page 12, second full paragraph the specification states:

The aldonic acid esters can be precipitated from the solution in the aprotic solvent [...] (*Emphasis added.*)

Claim 35 has been amended by replacing the term “polysaccharide derivative” with the term “optionally substituted polysaccharide”. Meaning of the term “optionally substituted polysaccharides”, as well as, possible substituents on a polysaccharides are well known to one of ordinary skill in the art. In addition, Claim 35 has been amended to more particularly point out the claimed embodiment.

Claims 36-41 have been amended by replacing noun and verb plurals with singular for clarification purposes.

Claims 36 and 41 have been amended by replacing the terms “polysaccharide derivative” and “starch fraction derivatives” with the terms “optionally substituted polysaccharide” and “optionally substituted starch fraction”, respectively. Meaning of terms “optionally substituted polysaccharides” and “optionally substituted starch fraction” as well as possible substituents on a polysaccharide are well known to one of ordinary skill in the art.

Claim 40 has been amended by deleting the term “greater than”.

Claims 39 and 40 have been amended by adding parentheses.

Claim 42 has been amended by adding the complete term “molar substitution” before the abbreviation “MS” and a parentheses around the abbreviation “MS”. Support for this amendment can be found on page 7, paragraph 6 of the specification.

Claim 45 has been amended correct an obvious typographical error by deleting repetition of the term “of the aldonic acid ester”.

Claim 47 has been amended to correct an obvious typographical error by replacing the recitation “N-hydroxysuccinimide and sulfo-N-hydroxysuccinimide” with the recitation “an N-hydroxysuccinimide or sulfo-N-hydroxysuccinimide”.

Claim 49 has been amended by replacing the term “comprising” with the term “consisting essentially off”. For details on this amendment the Examiner is referred to the section Support for Claims 49-52 Amendments, provided below.

Claims 50-52 have been amended by replacing the term “comprising” with the term “has”. For details on this amendment the Examiner is referred to the section Support for Claims 49-52 Amendments, provided below.

Claims 54-55, 58-59 and 68 have been amended by replacing the term “aldonic acid derivative” with the term “optionally substituted aldonic acid” and the term “polysaccharide derivative” with the term “optionally substituted polysaccharide”. Meaning of terms “optionally substituted polysaccharides” and “optionally substituted aldonic acid” as well as possible substituents on a polysaccharide and aldonic acid are well known to one of ordinary skill in the art.

Support for Claims 49-52 Amendments

Claim 49 is now amended to excludes all additional, unrecited elements that *materially affect* the basic properties of the recited aldonic ester from the solutions of at least one aldonic ester by replacing the transitional phrase “comprising” with the transitional phrase “consisting essentially of”. Pursuant to MPEP §2111.03:

The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (*emphasis in original*)

Thus, Claim 49, as amended, is directed to a solution of at least one aldonic acid ester of Claim 35 and any additional unrecited material that does *not materially* affect the characteristics of the claimed solution, for example, different solvents or water.

Dependent Claims 50-52 further specify the solvent of Claim 49. Therefore, Claims 50-52 also exclude any ingredient that could affect the basic properties of the solution as presented in Claim 49. Claims 50-52 have been amended by replacing the term “comprising” with the term “has”. Explanation of the transitional phrase “have” is given in MPEP §2111.03:

Transitional phrases such as "having" must be interpreted in light of the specification to determine whether open or closed claim language is intended.

In light of the dependency of Claims 50-52 on “closed-ended” Claim 49, transitional phrase “has” should be interpreted as a closed-ended phrase.

Election/Restriction

Applicants affirm provisional election with traverse of Group I (claims 35-53), drawn to an aldonic acid ester of polysaccharides, or polysaccharide derivatives, made in the telephone interview by Steven G. Davis on November 20, 2008. As indicated by Steven G. Davis in the above-mentioned telephone interview, traversal of the restriction requirement is maintained.

Rejection of Claims 35-53 under 35 U.S.C. §112, Second Paragraph

Claims 35-53 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner stated, that the term “derivative” renders these claims indefinite.

Claims 35-36 and 41 have been amended by replacing the term “polysaccharide derivatives” with the term “optionally substituted polysaccharides” and the term “starch fraction derivatives” with the term “optionally substituted starch fractions”. Applicants submit that the meaning of the terms “optionally substituted polysaccharide” or “optionally substituted starch fraction” as well as the permitted substituents on polysaccharides and starches are well known to one of ordinary skill in the art.

The Examiner stated that the recitation “in the range greater than 10 to 25 mol% α -1,6-glycosidic linkages” renders Claim 40 (erroneously referred to as Claim 38) indefinite.

Claim 40 has been amended by deleting the term “greater than”. Applicants submit that this amendment clarifies the range of an average branching to have an upper limit of 25 mol% and lower limit of 10 mol% α -1,6-glycosidic linkages.

The Examiner stated that recitation “MW” in claims 39, 40 and 42 renders these claims indefinite.

Claims 39, 40 and 42 have been amended by adding parentheses around the abbreviation “MW”. The complete term “molecular weight” is now preceding the abbreviation “MW”.

The Examiner stated that the recitation “MS” in Claim 42 renders Claim 42 indefinite.

Claim 42 has been amended by adding the complete term “molar substitution” before the abbreviation “MS” and a parentheses around the abbreviation “MS”.

The Examiner stated that the recitation “the alcohol component of the aldonic ester is derived is N-hydroxysuccinimide and sulfo-N-hydroxysuccinimide” renders Claim 47 indefinite. The Examiner further stated that it is unclear how the alcohol component of the aldonic ester can be derived from two compounds containing alcohol moiety when there is only one ester present in the aldonic acid ester compound.

Claim 47 has been amended to correct an obvious typographical error, by replacing the recitation “N-hydroxysuccinimide and sulfo-N-hydroxysuccinimide” with the recitation “an N-hydroxysuccinimide or sulfo-N-hydroxysuccinimide”. Applicants submit that the two compounds from which alcohol component of the aldonic ester can be derived, N-

hydroxysuccinimide and sulfo-N-hydroxysuccinimide, are used in the alternative. As noted by the Examiner, only one ester is formed in the reaction between aldonic acid and *either one* of these two alcohols.

Applicants submit that Claims 35-36, 39-42 and 47, as amended, are definite. Furthermore, Claims 37-38, 43-46 and 48-53, depend directly or indirectly on Claims 35-36, 39-42 and 47, and therefore, are also definite in view of the previously advanced rejection under 35 U.S.C. §112. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 35-38, 41, 43-46 and 49 under 35 U.S.C. §102(b)

Claims 35-38, 41, 43-46 and 49 have been rejected under 35 U.S.C. §102(b) as being anticipated by Sommermeyer *et al.*, an International Application publication WO 2002/080979 (hereinafter “Sommermeyer”), the U.S. National stage of which is published as U.S. Publication No. US 2005/0063943.

As stated by the Examiner (the paragraph bridging page 7 and 8 in the Office Action) Sommermeyer discloses in Example 2 (paragraph [0147]) a compound, which is a product of a coupling reaction between hydroxyethyl starch (HES) oxidized at the reducing end and Human Serum Albumin (HSA) protein. The reaction is proceeding in water, in the presence of ethyldimethyl-aminopropyl-carbodiimide (EDC). The Examiner stated that this coupling reaction and its product are further exemplified in Table 2 (page 11 of Sommermeyer). The Examiner asserts that an ester, as defined in the instant application on page 9 of the instant specification, is formed when an acid (oxidized hydroxyethyl starch (ox-HES)) is reacted with EDC in the presence of 1-hydroxy-1H-benzotriazolhydrate (1-HOBt). The Examiner is citing Marder *et al.*, “Industrial application of coupling reagents in peptides”, *Chimica Oggi* (Chemistry Today), 2003 (hereinafter, “Marder”), in support of his assertion.

Claim 35 has been amended to be directed to an *isolated* aldonic ester. Applicants submit that Table 2 of Sommermeyer teaches a *coupling* reaction between ox-HES and HSA. This reaction may proceed under various conditions, under some of which the “ester” as defined on page 9 of the instant specification, may not even form¹. In the course of the Sommermeyer’s

¹ See, *e.g.*, the title of the Table 2 of Sommermeyer, “Coupling reactions between HES (130 kD and 10 kD) with oxidized reducing end groups and HSA under *different* conditions” (*Emphasis added.*) Also see the synthetic schemes of FIG. 1 of Marder, which show different possible routes from the starting reactants to the final product.

reaction, the “ester” is an *intermediate* along the chemical route from an amino-containing HSA and a carboxyl-containing HES to the final coupled product that includes an amide bond (as evidenced by Marder, FIG. 1). Thus, the “ester” of Sommermeyer is not an *isolated* product, as claimed in independent Claim 35. The “ester” produced by Sommermeyer is *always in a mixture* with other reactants which would *materially affect* the basic properties of such an “ester”. Accordingly, base Claim 35 as well as claims dependent thereon are novel over Sommermeyer.

Furthermore, Claim 35, as amended, and claims dependent thereon are also non-obvious over Sommermeyer. There is no suggestion or motivation in Sommermeyer to isolate an aldonic ester from the mixtures described in Table 2 or in Example 2. Because even if produced, the “ester” of Table 2 is an intermediate, Sommermeyer does not provide any reason to isolate aldonic ester from the above-described mixtures. One of ordinary skill in the art would not be motivated by Sommermeyer’s teachings to isolate such an intermediate (aldonic ester) from the reaction mixture. Furthermore, Sommermeyer does not teach one of ordinary skill in the art how to obtain an isolated aldonic ester.

Therefore, Applicants submit that independent Claim 35, as amended, and Claims 36-38 and 43-46, dependant thereon, are novel and non-obvious over Sommermeyer. Reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) are respectfully requested.

Rejection of Claims 39, 40 and 42 under 35 U.S.C. §103(a)

Claims 39, 40 and 42 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Sommermeyer as applied to Claims 35-38, 41, 43-46 and 49 above.

The Examiner stated that it would have been obvious to one of ordinary skill in the art to use the aldonic esters of Sommermeyer to optimize the C2/C6 ratio and the degree of branching of starch fractions.

Applicants submit that independent Claim 35, as amended, is novel and non-obvious over Sommermeyer, for the reasons discussed in the preceding section of this reply. Claims 39, 40 and 42 depend indirectly on Claim 35, and therefore, are also novel and non-obvious over Sommermeyer.

Reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) are respectfully requested.

Rejection of Claims 47, 48 and 50-53 under 35 U.S.C. §103(a)

Claims 47, 48 and 50-53 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Sommermeyer as applied to Claims 35-38, 41, 43-46 and 49 above, further in view of chapter entitled "Zero-Length Cross-linkers" by G. T. Hermanson, Bioconjugate Techniques, page 170-180, 1999 (hereinafter, "Hermanson").

The Examiner stated that it would have been obvious to one of ordinary skill in the art to combine teachings of Sommermeyer, concerning a conjugate of hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxyl starch is coupled to the active ingredient either directly or via a linker using EDC, with the teaching of Hermanson, regarding the use of EDC/sulfo-N-hydroxysuccinimide (sulfo-NHS) in a conjugation reaction as an alternative to EDC.

Applicants submit that independent Claim 35, as amended, is novel and non-obvious over Sommermeyer, for reasons discussed in the preceding section of this reply. Claims 47, 48 and 50-53 depend directly or indirectly on Claim 35, and therefore, are also novel and non-obvious over Sommermeyer. Without going into further merits of Hermanson, Applicants note that it does not teach isolated aldonic ester. Therefore it does not remedy the deficiency of Sommermeyer.

In the view of above, Claims 47, 48 and 50-53 are non-obvious over Sommermeyer in view of Hermanson. Reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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